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Research Article

A Study Of The Heterocyclic Benzoxazole Derivatives Design, Synthesis, And Anti-Fungal Assessment

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ARTICLE INFO

ABSTRACT

A family of heterocyclic molecules having a variety of pharmacological actions, including antifungal qualities, are benzoxazole derivatives. The development of innovative antifungal drugs with enhanced effectiveness and decreased resistance is imperative due to the rise in fungal infections and the advent of drug-resistant strains. The design, synthesis, and antifungal evaluation of benzoxazole derivatives as possible antifungal drugs are examined in this work. A range of benzoxazole derivatives were created to investigate the structure-activity correlations influencing their antifungal efficacy via the use of molecular modeling tools. The suggested compounds were prepared using synthetic techniques, and their antifungal efficacy against therapeutically relevant fungal strains was later assessed. To evaluate the synthetic compounds' selectivity and safety profile, cytotoxicity experiments were carried out.

Keyword: benzoxazole, Heterocyclic

1. INTRODUCTION

Benzoxazole derivatives have garnered significant interest in the field of medicinal chemistry owing to their diverse pharmacological activities. These heterocyclic compounds are characterized by a benzene ring fused with an oxazole ring, rendering them structurally versatile and potentially bioactive. Their pharmacological profile spans a wide range of activities including antibacterial, antiviral, anticancer, anti-inflammatory, and antifungal properties. Fungal infections pose a significant threat to human health, particularly in immunocompromised individuals and those with underlying medical conditions. The emergence of drug-resistant fungal strains has further exacerbated the challenge of treating these infections effectively. [1]
Benzoxazoles are important members of the family of fused heterocycles that have attracted much attention because of their diverse biological activity. In order to find new potential pesticide molecules with antifungal activities, we designed and synthesized a series of benzoxazole derivatives and evaluated their potential antifungal activities against eight kinds of plant pathogenic fungus commonly found in agriculture systematically, including Fusarium solani, Colletotrichum gloeosporioides, Mycosphaerella melonis, Alternaria brassicae, Pyricularia grisea, Curvularia lunata, Alternaria solani, and Fusarium graminearum. As Scheme 1 shows, namely the synthesis of benzoxazoles can be classified into two kinds: one is using PPA as solvent and catalyst at the presence of acid and aniline in one step the other is using condensation of aldehyde and aniline then an oxidation step using some oxidizer such as DDQ, Manganese oxide, air, etc. Our research group has been intensively studying the synthesis of heterocycles and their agricultural applications. Pyridine, also known as azabenzene, has a certain aromatic structure and is widely used in sulfonamides and pesticides. Inspired by three molecules used as agrichemicals in Figure 1, we envisioned a combination of pyridine, benzoxazole, and amide might have good antifungal activities against plant pathogen. Prompted by the above thoughts, we wish to report the synthesis, spectroscopic, single-crystal diffraction, antifungal activity, of a series of benzoxazoles bearing a pyridine ring and amide moiety. In our devise, the two heterocyclic moiety contributes the biological activities, and the amide would tune the activities.[2]

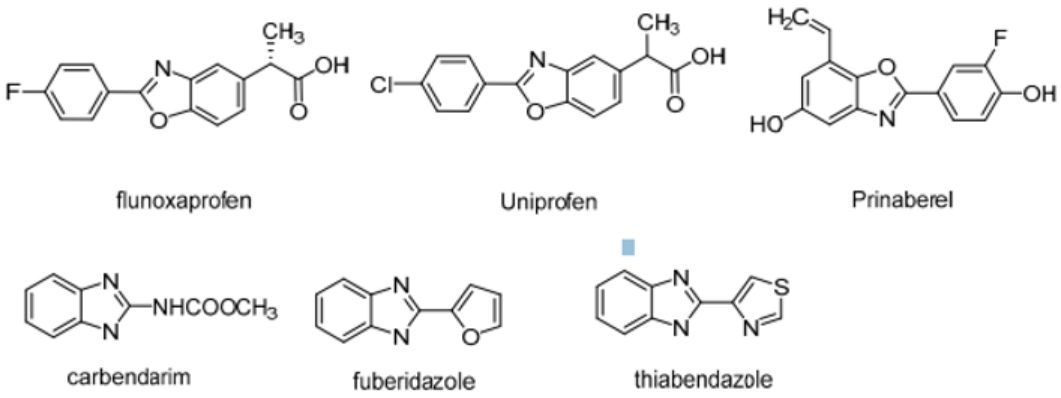
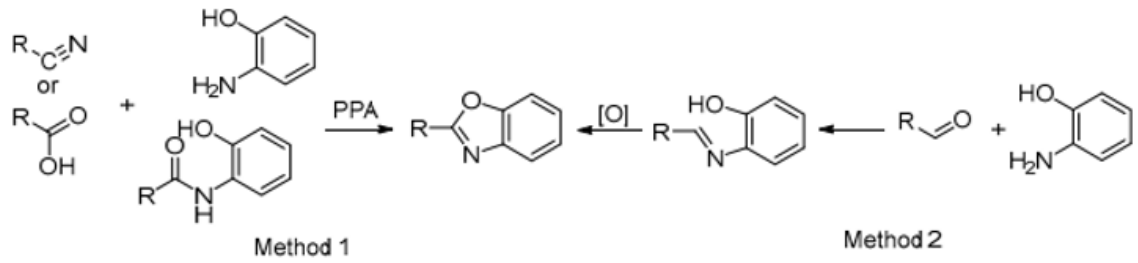


Figure 1: Typical compounds of benzoxazoles



Scheme 1 : The syntheses of benzoxazoles

2. LITERATURE REVIEW

Sweta Joshi, Ajay Singh Bisht and Divya Juyal (2017) Oxazole contain an oxygen atom and a pyridine type nitrogen atom at the 1 and 3 positions of the ring and like pyridine, oxazole are weekly basic substances. Oxazole be considered as derived from furan by the replacement of –CH= (methane group) from the position-3 by the azomethine nitrogen (-N=) group. Oxazole is a heterocyclic compound and exhibits a wide variety of pharmacological activities such as analgesics, anti-inflammatory, antimicrobial, anticancer, antidepressants, antidiabetic and antiobesity, anticonvulsant, diuretics and anticancer. Differently substituted oxazole moieties have different activity. In this article we discussed about oxazole chemistry, properties, naturally occurring oxazoles, synthesis, reactions and several pharmacological activities.[3]

B. S. Rawat, Shrawan Shukla (2016) The Benzimidazoles, 1,2,4 triazoles, thiazolidinones, oxadiazoles, pyridine and pyrimidine nucleus has diverse pharmacological activities such as antibacterial, anthelmintic, antifungal etc. The thiazole nucleus is also known to possess various biological activities viz. antidepressant, hypertrophy, cardiac, bactericidal, anaesthetic and antifungal activity. The aim of this work is to study the effect of three methoxy group on the course of the reaction with substituted thiazole/oxazole nucleus and on the antibacterial & antifungal activity of the synthesized products. The synthesized compounds were investigated against Staphylococcus aureus, B.subtilis, P. Aeruginosa, and E.coli for antibacterial study and against C. Albicans, Aspergillus Niger for antifungal activity.[4]

Kakkar, S., Tahlan, S., Lim, S.M. et al.(2018) A new series of benzoxazole analogues was synthesized and checked for their in vitro antibacterial, antifungal and anticancer activities. The synthesized benzoxazole compounds were confirmed by IR, 1H/13C-NMR, mass and screened for their in vitro antimicrobial activity against Gram-positive bacterium: Bacillus subtilis, four Gram-negative bacteria: Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumoniae, Salmonella typhi and two fungal strains: Candida albicans and Aspergillus niger using tube dilution technique and minimum inhibitory concentration (MIC) was noted in μM and compared to ofloxacin and fluconazole. Human colorectal carcinoma (HCT116) cancer cell line was used for the determination of in vitro anticancer activity (IC50 value) by Sulforhodamine B assay using 5-fluorouracil as standard drug.[5]

Mehlika Dilek ALTINTOP, Gülşen AKALIN ÇİFTÇİ, Halide Edip TEMEL (2017) Gliomas account for the majority of human brain tumors and the incidence of gliomas is expected to rise in upcoming years and therefore extensive efforts have been devoted to the discovery of potent antiglioma agents. Due to the importance of benzoxazoles for anticancer drug discovery, herein new benzoxazole-based hydrazone derivatives (3a-g) were designed and synthesized. The cytotoxic effects of the compounds on C6 rat glioma and NIH/3T3 mouse embryonic fibroblast cell lines were investigated using MTT assay. The apoptotic effects of the most selective anticancer agent were analyzed based on Annexin V-PI binding capacities in flow cytometry.[6]

Rashmi Rana and Anam Ansar (2023) Heterocyclic compounds are an important class of organic compound. Owing to their usefulness in synthetic processes, numerous heterocyclic compounds are currently known, and this number is growing quickly. The uses of heterocyclic compounds are numerous. They are mostly used as veterinary goods, agricultural chemicals, and medications. Additionally, they are used as sanitizers, cleansers, antioxidants, corrosion inhibitors, co-polymers, and dye ingredients. The ring of a heterocyclic compound contains at least two unique components as members. On such a cyclic ring, the frequent heteroatoms are oxygen, nitrogen as well as sulphur. The most stable heterocyclic compound is a 7-membered ring over other heterocyclic compounds.[7]

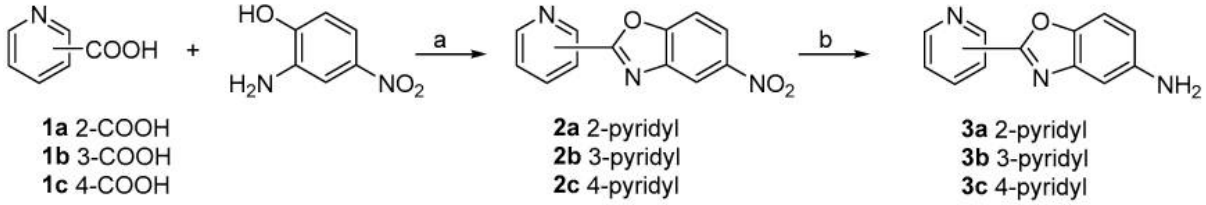
3. RESEARCH METHODOLOGY

In order to discover more promising anti-fungal agents, a series of benzoxazole family was synthesized by PPA-catalyzed condensation and a Raney nickel/hydrazine reduction. Altogether 45 compounds were obtained in good to excellent yields and characterized by FT-IR, NMR, MS, and X-ray crystal diffraction. Moreover, the biological activity against eight phytopathogenic fungi was investigated. All in all, most of these compounds bear moderate antifungal activities. Among them, three candidates show the strongest activities, compound 4ac, 4bc provided over 50% inhibition rate against five fungi. Especially, the inhibitory rate of compound 4ah on Mycosphaerella melonis reached 76.4%

4. DATA ANALYSIS

4.1 Chemistry

As shown in Scheme 2, the isomers (2-, 3-, 4-, respectively) of picolinic acid condensed with 4-nitro-2-aminophenol at the presence of PPA to provide the three types of pyridyl-benzoxazole in 75–85% yield. Compared with the reported method, the PPA was preheated to 80 °C before use in order to be measured easily. Next, a mild reduction in the nitro group to amino group was adopted using hydrazine and Raney nickel in 75–80% yield. The other reduction methods proved unsuccessful, such as palladium/carbon catalytic hydrogenation, stannous chloride in common solvent (ethyl acetate and tetrahydro furan), and iron powder in acetic acid. A lot of black tar which can be solved in acidic condition was produced under these conditions. We suspected that the oxales ring was opened upon these conditions. As to the preparation of the nitro-benzoxazoles, there is another nitration method of benzoxazole, but the nitro group position is limited to the para- to the OH group. Next, we condensed three pyridyl-benzoxazole compounds with 15 different types of acyl chlorides to obtain 45 amide derivatives (4aa–4co) in fairly good to excellent yield (Table 1) and were characterized by 1H NMR and 13C NMR. The stereochemistry of two compounds 4ac and 4bc with the best antifungal effect was further confirmed by the X-ray crystallographic analysis (Figure 2).[8]



Scheme 2: The preparation of benzoxazoles. (a: PPA, 140–150 °C, 6–8 h; b: W-2 Raney Ni, NH2NH2, 60 °C, 5 h).

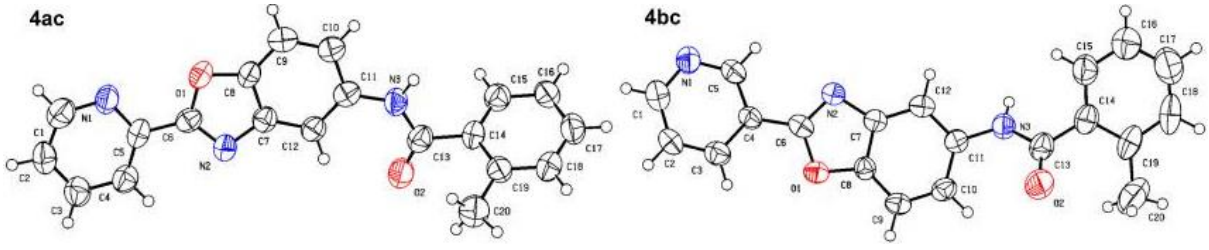


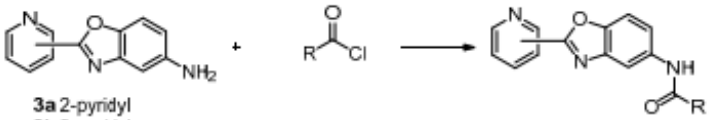
Figure 2: X-ray crystallographic structures of 4ac and 4bc.

4.2. X-ray Crystallographic Studies of 4ac, 4bc

Compound 4ac crystallizes in the monoclinic space group P21. There are two crystallographic independent molecules in the asymmetric unit (only one of them is shown in Figure 2). In the molecule of 4ac, bond lengths and angles are very similar to those provided in the literature for benzoxazole derivative. The benzoxazole ring was approximately planar. Compared with the 4bc, the dihedral angle between the methylphenyl plane and the oxazole ring was 55.65°. Compound 4bc crystallizes in the monoclinic space group C2/c. There are eight crystallographic independent molecules in the asymmetric unit (only one of them is shown in Figure 2). In the molecule of 4bc, bond lengths and angles are very similar to those provided in the literature for benzoxazole

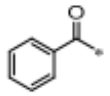
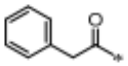
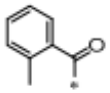
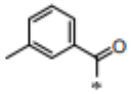
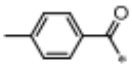
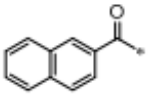
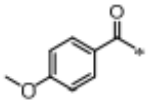
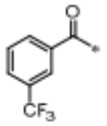
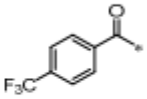
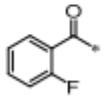
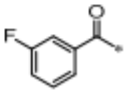
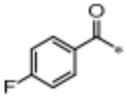
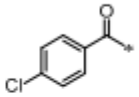
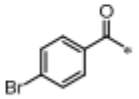
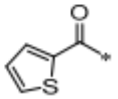
derivative. The whole molecule was approximately planar. The dihedral angle of the methylphenyl plane, the oxazole ring, was 8.61°. X-ray diffraction reflection data of 4ac and 4bc are shown in the Supplementary Materials.

Table 1: The syntheses of amide derivatives of benzoxazoles



3a 2-pyridyl
3b 3-pyridyl
3c 4-pyridyl

4aa-4co

Entry	2-Pyridyl	3-Pyridyl	4-Pyridyl	R[a]
1	4aa	4ba	4ca	
2	4ab	4bb	4cb	
3	4ac	4bc	4cc	
4	4ad	4bd	4cd	
5	4ae	4be	4ce	
6	4af	4bf	4cf	
7	4ag	4bg	4cg	
8	4ah	4bh	4ch	
9	4ai	4bi	4ci	
10	4aj	4bj	4cj	
11	4ak	4bk	4ck	
12	4al	4bl	4cl	
13	4am	4bm	4cm	
14	4an	4bn	4cn	
15	4ao	4bo	4co	

4.3. In Vitro Anti-Fungal Activity

Meanwhile, the anti-fungal activities of these compounds were evaluated against eight common phytopathogenic fungi, (Fusarium solani, Colletotrichum gloeosporioides, Mycosphaerella melonis, Alternaria brassicae, Pyricularia grisea, Curvularia lunata, Alternaria solani, and Fusarium graminearum) using the inhibition zone method at the concentration of 100 μg/mL by the poisoned food technique. While thiophanate-methyl, which is a fungicide bearing similar heterocyclic structures and a commercially available agricultural fungicide, was used as a positive control at 100 μg/mL. As shown in Figure 3, the experiments revealed that most of these compounds bears moderate result to Colletotrichum gloeosporioides and Mycosphaerella melonis. Through the 3D -Bar of inhibition rate against eight fungi, we could see, compound 4ac, 4bc showed best results, providing over 50% inhibition rate against five fungi. Herein, we believe the methyl makes a rotation barrier, and to some extent enhances the combination of compound to the enzyme. Interestingly, some compounds could selectively inhibit some fungi. For example, the inhibitory rate of compound 4ah on Mycosphaerella melonis could reach 76.4%, but it had little inhibitory activity on other fungi. Another example was that compound 4bh could highly selectively inhibit the growth of Alternaria brassicae. However, 4be against Fusarium solani, 4cj and 4af against Colletotrichum gloeosporioides provided unsatisfactory results, even positive results. From the whole table, the effect of acyl ligand on antifungal activity was greater than that of pyridyl-benzoxazole skeleton. Typical examples are compounds 4ac and 4bc, and even compound 4cc, which have very good antifungal activity and all of them have the same acyl ligand.[9]

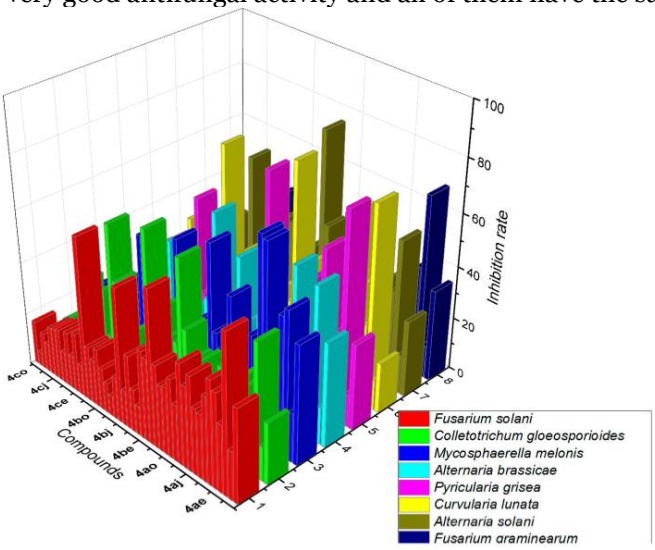


Figure 3: Antifungal activities of compounds 4aa–4co at 100 μg/mL.

5. Supplies and Procedures

All chemicals were purchased from Energy chemicals and Merck (used without further purification). The melting point was determined using a digital melting point meter WRS-1B. The 1H NMR and 13C NMR spectra were carried out by AV 500 MHz spectrometer. X-ray analysis of the samples were recorded on a Bruker APEX II area detector diffractometer at 296(2) K with a graphite-monochromatic MoK radiation (λ = 0.71073A°).

5.1.1. General Synthesis of 3a–3c

5-Nitro-2-(pyridin-2-yl)benzo[d]oxazole (3a). To a solution of 2-picolinic acid (2.46 g 0.01 mol) condensed with 4-nitro-2-aminophenol (3.08 g, 0.01 mol) in polyphosphoric acid (30 mL) in a 100mL three-necked flask, the middle neck was installed a mechanical stirring, and the side neck was set for thermometer. The reaction mixture was heated 140 °C and the external temperature was kept at 150 °C. After 6 h, the reaction was completed through TLC. Then the reaction mixture was poured into water slowly and was adjusted to pH 6 using potassium carbonate. A quantity of solid precipitated and was collected by suction. This compound was used without further purification and drying. Because the next reduction was carried out in ethyl alcohol, the crude product 2a was used directly. The crude 2a was dissolved in 95% ethyl alcohol (40 mL), and then was added W-2 Raney nickel (ca. 0.20 g), and then hydrazine (1.96 g, 3 equiv.) was introduced drop wise. Moreover, the mixture was heated to 60 °C and monitored by TLC. After completion, the reaction mixture was filtered through a Celite pad. The filtration was condensed and purified by flash column chromatography (petroleum ether: ethyl acetate) to obtain 3a (1.94 g, 72% for two steps) as a brown solid: 1H NMR (500 MHz, DMSO) δ 8.78 (d, J = 4.1 Hz, 1H), 8.29 (d, J = 7.9 Hz, 1H), 8.05 (dd, J = 10.9, 4.5 Hz, 1H), 7.61 (dd, J = 6.9, 5.1 Hz, 1H), 7.49 (d, J = 8.7 Hz, 1H), 6.95 (d, J = 1.6 Hz, 1H), 6.77 (dd, J = 8.7, 1.9 Hz, 1H), 5.19 (s, 2H); 13C NMR (126 MHz, DMSO) δ 161.53, 150.55, 147.35, 146.12, 143.46, 142.78, 138.02, 126.21, 123.63, 114.66, 111.38, 103.16.
2-(Pyridin-3-yl)benzo[d]oxazol-5-amine (3b) and 2-(pyridin-4-yl)benzo[d]oxazol-5-amine (3c) could be obtained in same procedure as a brown solid in a similar yield, respectively.

Compound 3b: 1H NMR (500 MHz, DMSO) δ 9.31 (s, 1H), 8.79 (s, 1H), 8.48 (d, J = 6.7 Hz, 1H), 7.64 (s, 1H), 7.48 (d, J = 8.6 Hz, 1H), 6.93 (s, 1H), 6.74 (d, J = 8.6 Hz, 1H), 5.21 (s, 2H); 13C NMR (126 MHz, DMSO) δ 160.40, 152.31, 148.16, 147.35, 143.20, 142.75, 134.80, 124.72, 123.69, 114.18, 111.18, 103.03.
Compund 3c: 1H NMR (500 MHz, DMSO) δ 8.83 (d, J = 5.6 Hz, 2H), 8.05 (d, J = 5.7 Hz, 2H), 7.51 (d, J = 8.7 Hz, 1H), 6.95 (d, J = 1.7 Hz, 1H), 6.79 (dd, J = 8.7, 1.9 Hz, 1H), 5.27 (s, 2H); 13C NMR (126 MHz, DMSO) δ 160.31, 151.26, 147.53, 143.37, 142.76, 134.33, 120.97, 115.06, 111.41, 103.07.

5.1.2. General Procedures for the Synthesis of 4aa–4co

Typical synthesis procedure of amide, taking 4aa as an example: to a vial (20 mL) was charged THF (5 mL), and then 3a (0.02 g, 1 mmol) and benzoyl chloride (0.17 mL) and catalytical amount of DMAP. Thus, the reaction mixture was stirred for 6 h. Moreover, the reaction mixture was poured into water (50 mL) and the precipitate was collected by suction.[10] After recrystallization in ethyl acetate, the target molecules could be obtained in 75–92% yield. The detailed characterization of NMR and spectrum are attached as follows:

N-(2-(Pyridin-2-yl)benzo[d]oxazol-5-yl)benzamide (4aa)

Yield 65.3%; Pink solid; mp 138.1–138.5 °C; 1H NMR (500 MHz, DMSO) δ 10.49 (s, 1H), 8.84 (d, J = 4.2 Hz, 1H), 8.39 (d, J = 11.0 Hz, 2H), 8.10 (td, J = 7.8, 1.4 Hz, 1H), 8.01 (dd, J = 27.5, 7.2 Hz, 2H), 7.86 (s, 2H), 7.68–7.64 (m, 2H), 7.61–7.51 (m, 2H).13C NMR (126 MHz, DMSO) δ 166.17, 150.71, 147.41, 145.73, 141.85, 138.18, 137.08, 135.37, 132.13, 129.74, 128.92, 128.18, 126.70, 124.10, 120.13, 112.10, 111.49.

2-Phenyl-N-(2-(pyridin-2-yl)benzo[d]oxazol-5-yl)acetamide (4ab)

Yield 37.4%; Pink solid; mp 120.6–120.8 °C; 1H NMR (500 MHz, DMSO) δ 10.46 (s, 1H), 8.82 (d, J = 4.1 Hz, 1H), 8.35 (d, J = 7.9 Hz, 1H), 8.26 (s, 1H), 8.08 (dd, J = 11.0, 4.4 Hz, 1H), 7.80 (d, J = 8.8 Hz, 1H), 7.67–7.62 (m, 2H), 7.38 (dd, J = 13.4, 6.0 Hz, 4H), 7.29 (t, J = 7.0 Hz, 1H), 3.72 (s, 2H).13C NMR (126 MHz, DMSO) δ 169.70, 162.46, 150.68, 147.05, 145.70, 141.90, 138.15, 137.19, 136.42, 129.65, 128.81, 127.05, 126.67, 124.07, 118.84, 111.62, 110.70, 43.80.

2-Methyl-N-(2-(pyridin-2-yl)benzo[d]oxazol-5-yl)benzamide (4ac)

Yield 56.8%; Pink solid; mp 168.1–168.9 °C; 1H NMR (500 MHz, DMSO) δ 10.46 (s, 1H), 8.83 (d, J = 4.1 Hz, 1H), 8.38 (d, J = 10.0 Hz, 2H), 8.10 (t, J = 7.7 Hz, 1H), 7.87–7.82 (m, 4H), 7.69–7.65 (m, 1H), 7.47 (d, J = 6.6 Hz, 2H), 2.45 (s, 3H).13C NMR (126 MHz, DMSO) δ 166.27, 162.47, 150.71, 147.37, 145.73, 141.83, 138.24, 138.19, 137.13, 135.36, 132.70, 128.82, 128.66, 126.70, 125.34, 124.09, 120.10, 112.05, 111.47, 21.47.

3-Methyl-N-(2-(pyridin-2-yl)benzo[d]oxazol-5-yl)benzamide (4ad)

Yield 26.8%; Pink solid; mp 179.2–179.7 °C; 1H NMR (500 MHz, DMSO) δ 10.55 (s, 1H), 8.83 (d, J = 4.1 Hz, 1H), 8.44–8.31 (m, 2H), 8.09 (td, J = 7.8, 1.5 Hz, 1H), 7.83 (q, J = 8.8 Hz, 2H), 7.67 (dd, J = 6.6, 4.9 Hz, 1H), 7.54 (d, J = 7.2 Hz, 1H), 7.44 (t, J = 7.1 Hz, 1H), 7.35 (t, J = 7.5 Hz, 2H), 2.45 (s, 3H).13C NMR (126 MHz, DMSO) δ 168.41, 162.49, 150.71, 147.29, 145.72, 141.89, 138.18, 137.64, 137.24, 135.78, 131.05, 130.18, 127.75, 126.69, 126.16, 124.09, 119.34, 111.57, 111.26, 19.82.

4-Methyl-N-(2-(pyridin-2-yl)benzo[d]oxazol-5-yl)benzamide (4ae)

Yield 43.4%; Pink solid; mp 212.2–212.8 °C; 1H NMR (500 MHz, DMSO) δ 10.45 (s, 1H), 8.83 (d, J = 4.1 Hz, 1H), 8.41–8.35 (m, 2H), 8.09 (t, J = 7.6 Hz, 1H), 7.96 (d, J = 7.9 Hz, 2H), 7.90–7.81 (m, 2H), 7.66 (dd, J = 6.9, 5.0 Hz, 1H), 7.38 (d, J = 7.9 Hz, 2H), 2.42 (s, 3H).13C NMR (126 MHz, DMSO) δ 165.96, 162.43, 150.69, 147.32, 145.73, 142.13, 141.82, 138.16, 137.18, 132.45, 129.42, 128.24, 126.67, 124.07, 120.14, 112.07, 111.41, 21.51.

N-(2-(Pyridin-2-yl)benzo[d]oxazol-5-yl)-2-naphthamide (4af)

Yield 37.8%; Pink solid; mp 182.4–182.9 °C; 1H NMR (500 MHz, DMSO) δ 10.83 (s, 1H), 8.84 (d, J = 4.2 Hz, 1H), 8.71 (s, 1H), 8.47 (d, J = 10.5 Hz, 1H), 8.39 (d, J = 7.8 Hz, 1H), 8.16–8.08 (m, 4H), 8.05 (d, J = 7.7 Hz, 1H), 7.95 (dd, J = 8.8, 1.5 Hz, 1H), 7.88 (d, J = 8.8 Hz, 1H), 7.72–7.61 (m, 3H).13C NMR (126 MHz, DMSO) δ 166.22, 162.48, 150.71, 147.41, 145.74, 141.87, 138.18, 137.24, 134.81, 132.62, 129.49, 128.60, 128.51, 128.17, 127.81, 127.33, 126.69, 126.01, 124.99, 124.09, 120.19, 112.14, 111.50.

4-Methoxy-N-(2-(pyridin-2-yl)benzo[d]oxazol-5-yl)benzamide (4ag)

Yield 70.1%; Pink solid; mp 199.1–199.8 °C; 1H NMR (500 MHz, DMSO) δ 10.32 (s, 1H), 8.83 (d, J = 4.0 Hz, 1H), 8.38 (d, J = 3.7 Hz, 2H), 8.10 (t, J = 7.6 Hz, 1H), 8.04 (d, J = 8.6 Hz, 2H), 7.84 (s, 2H), 7.67 (dd, J = 6.9, 5.1 Hz, 1H), 7.12 (d, J = 8.7 Hz, 2H), 3.89 (s, 3H).13C NMR (126 MHz, DMSO) δ 165.52, 162.47, 162.43, 150.71, 147.28, 145.75, 141.84, 138.18, 137.26, 130.12, 127.36, 126.68, 124.08, 120.13, 114.15, 112.03, 111.41, 55.95.

N-(2-(Pyridin-2-yl)benzo[d]oxazol-5-yl)-3-(trifluoromethyl)benzamide (4ah)

Yield 52.3%; Pink solid; mp 137.9–138.5 °C; 1H NMR (500 MHz, DMSO) δ 10.82 (s, 1H), 8.83 (s, 1H), 8.39 (d, J = 9.9 Hz, 3H), 8.19 (s, 1H), 8.10 (t, J = 6.9 Hz, 1H), 8.01 (d, J = 6.9 Hz, 1H), 7.89–7.77 (m, 3H), 7.67–7.62 (m, 1H).13C NMR (126 MHz, DMSO) δ 164.66, 162.56, 150.71, 147.60, 145.69, 141.85, 138.18, 136.71, 136.22, 133.34, 132.37, 130.23, 129.22, 128.68, 126.72, 124.80, 124.11, 120.33, 112.43, 111.56.

N-(2-(Pyridin-2-yl)benzo[d]oxazol-5-yl)-4-(trifluoromethyl)benzamide (4ai)
Yield 42.7%; Pink solid; mp 146.0–146.6 °C; 1H NMR (500 MHz, DMSO) δ 10.70 (s, 1H), 8.83 (d, J = 4.2 Hz, 1H), 8.43–8.35 (m, 2H), 8.22 (d, J = 8.0 Hz, 2H), 8.08 (tt, J = 12.1, 6.0 Hz, 1H), 7.96 (d, J = 8.1 Hz, 2H), 7.90–7.85 (m, 2H), 7.66 (dd, J = 6.9, 5.1 Hz, 1H).13C NMR (126 MHz, DMSO) δ 166.68, 164.97, 162.56, 150.69, 147.59, 145.69, 141.86, 139.15, 138.15, 136.69, 130.58, 129.12, 126.70, 125.88, 124.10, 120.16, 112.26, 111.57.

2-Fluoro-N-(2-(pyridin-2-yl)benzo[d]oxazol-5-yl)benzamide (4aj)
Yield 22.6%; Pink solid; mp 231.2–231.9 °C; 1H NMR (500 MHz, DMSO) δ 10.70 (s, 1H), 8.83 (s, 1H), 8.38 (s, 2H), 8.09 (s, 1H), 7.88–7.68 (m, 5H), 7.39 (d, J = 7.4 Hz, 2H).13C NMR (126 MHz, DMSO) δ 163.37, 162.57, 150.71, 147.44, 145.68, 141.90, 138.19, 136.82, 133.12, 133.06, 130.44, 126.73, 125.08, 124.11, 119.44, 116.78, 116.61, 111.70, 111.42.

3-Fluoro-N-(2-(pyridin-2-yl)benzo[d]oxazol-5-yl)benzamide (4ak)
Yield 62.8%; Pink solid; mp 174.5–175.4 °C; 1H NMR (500 MHz, DMSO) δ 8.83 (s, 1H), 8.38 (d, J = 11.4 Hz, 2H), 8.09 (t, J = 7.1 Hz, 1H), 7.92–7.79 (m, 4H), 7.65 (d, J = 6.2 Hz, 2H), 7.52–7.35 (m, 2H).13C NMR (126 MHz, DMSO) δ 164.74, 163.42, 162.52, 161.48, 150.70, 147.52, 145.69, 141.84, 138.17, 136.79, 131.06, 126.70, 124.10, 120.20, 118.93, 116.09, 114.94, 112.25, 111.53.

4-Fluoro-N-(2-(pyridin-2-yl)benzo[d]oxazol-5-yl)benzamide (4al)
Yield 23.7%; Pink solid; mp 168.0–168.7 °C; 1H NMR (500 MHz, DMSO) δ 10.56 (s, 1H), 8.83 (d, J = 4.2 Hz, 1H), 8.37 (d, J = 7.5 Hz, 2H), 8.10 (ddd, J = 9.1, 8.2, 3.5 Hz, 3H), 7.87–7.80 (m, 2H), 7.66 (dd, J = 7.1, 5.0 Hz, 1H), 7.41 (t, J = 8.8 Hz, 2H).13C NMR (126 MHz, DMSO) δ 165.60, 165.05, 163.62, 162.49, 150.70, 147.43, 145.71, 141.84, 138.17, 136.98, 130.90, 126.69, 124.09, 120.18, 115.76, 112.18, 111.49.

4-Chloro-N-(2-(pyridin-2-yl)benzo[d]oxazol-5-yl)benzamide (4am)
Yield 32.1%; Pink solid; mp 201.9–202.3 °C; 1H NMR (500 MHz, DMSO) δ 10.63 (s, 1H), 8.83 (d, J = 4.2 Hz, 1H), 8.37 (d, J = 9.4 Hz, 2H), 8.11–8.06 (m, 3H), 7.88–7.84 (m, 2H), 7.66 (t, J = 7.9 Hz, 3H).13C NMR (126 MHz, DMSO) δ 165.04, 162.50, 150.70, 147.48, 145.70, 141.83, 138.17, 136.96, 136.89, 134.03, 130.17, 128.97, 126.70, 124.09, 120.18, 112.21, 111.50.

4-Bromo-N-(2-(pyridin-2-yl)benzo[d]oxazol-5-yl)benzamide (4an)
Yield 43.2%; Pink solid; mp 284.5–285.1 °C; 1H NMR (500 MHz, DMSO) δ 10.69 (s, 1H), 8.83 (d, J = 4.1 Hz, 1H), 8.39–8.36 (m, 1H), 8.09 (dd, J = 10.9, 4.5 Hz, 1H), 8.01 (d, J = 8.4 Hz, 2H), 7.86 (s, 2H), 7.78 (d, J = 8.4 Hz, 2H), 7.66 (dd, J = 7.1, 5.1 Hz, 1H), 7.47 (d, J = 8.2 Hz, 1H).13C NMR (126 MHz, DMSO) δ 165.17, 162.49, 150.70, 147.47, 145.70, 141.83, 138.17, 136.91, 134.40, 131.90, 130.37, 126.69, 125.88, 124.09, 120.20, 112.22, 111.49.

N-(2-(Pyridin-2-yl)benzo[d]oxazol-5-yl)thiophene-2-carboxamide (4ao)
Yield 72.3%; Pink solid; mp 140.3–140.7 °C; 1H NMR (500 MHz, DMSO) δ 10.46 (s, 1H), 8.83 (s, 1H), 8.40–8.32 (m, 2H), 8.10 (s, 2H), 7.92–7.79 (m, 3H), 7.67 (s, 1H), 7.28 (s, 1H).13C NMR (126 MHz, DMSO) δ 162.53, 160.52, 150.70, 147.47, 145.70, 141.89, 140.37, 138.18, 136.59, 132.44, 129.73, 128.57, 126.71, 124.11, 120.15, 112.21, 111.57.

N-(2-(Pyridin-3-yl)benzo[d]oxazol-5-yl)benzamide (4ba)
Yield 36.9%; Pink solid; mp 152.1–152.7 °C; 1H NMR (500 MHz, CDCl3) δ 10.48 (s, 1H), 9.34 (s, 1H), 8.79 (s, 1H), 8.52 (d, J = 6.9 Hz, 1H), 8.32 (s, 1H), 7.97 (d, J = 6.3 Hz, 2H), 7.79 (s, 2H), 7.65–7.52 (m, 4H).13C NMR (126 MHz, CDCl3) δ 165.72, 161.05, 152.39, 147.99, 146.70, 141.37, 136.61, 134.88, 131.69, 128.45, 127.71, 124.31, 122.85, 119.28, 111.43, 111.29, 110.82.

2-Phenyl-N-(2-(pyridin-3-yl)benzo[d]oxazol-5-yl)acetamide (4bb)
Yield 47.2%; Pink solid; mp 110.9–111.6 °C; 1H NMR (500 MHz, DMSO) δ 10.48 (s, 1H), 9.36 (s, 1H), 8.83 (s, 1H), 8.55 (d, J = 6.8 Hz, 1H), 8.23 (s, 1H), 7.79 (d, J = 8.6 Hz, 1H), 7.70–7.58 (m, 2H), 7.41–7.23 (m, 5H), 3.72 (s, 2H).13C NMR (126 MHz, DMSO) δ 169.71, 161.50, 152.81, 148.46, 146.82, 141.90, 137.20, 136.40, 135.23, 129.67, 128.83, 127.07, 124.82, 123.30, 118.43, 111.44, 110.41, 43.79.

2-Methyl-N-(2-(pyridin-3-yl)benzo[d]oxazol-5-yl)benzamide (4bc)
Yield 29.8%; Pink solid; mp 158.1–158.8 °C; 1H NMR (500 MHz, DMSO) δ 10.56 (s, 1H), 9.41 (s, 1H), 8.87 (s, 1H), 8.63 (d, J = 6.9 Hz, 1H), 8.37 (s, 1H), 7.85–7.73 (m, 3H), 7.54 (d, J = 6.8 Hz, 1H), 7.44 (d, J = 7.0 Hz, 1H), 7.36 (d, J = 7.3 Hz, 2H), 2.45 (s, 3H).13C NMR (126 MHz, DMSO) δ 168.41, 161.29, 152.17, 147.92, 147.05, 141.86, 137.60, 137.28, 135.92, 135.76, 131.05, 130.21, 127.75, 126.17, 125.12, 123.57, 119.01, 111.42, 110.98, 19.82.

3-Methyl-N-(2-(pyridin-3-yl)benzo[d]oxazol-5-yl)benzamide (4bd)
Yield 36.8%; Pink solid; mp 179.1–179.7 °C; 1H NMR (500 MHz, DMSO) δ 10.55 (s, 1H), 9.39 (s, 1H), 8.84 (s, 1H), 8.57 (d, J = 7.2 Hz, 1H), 8.38 (s, 1H), 7.85 (s, 3H), 7.70 (d, J = 14.2 Hz, 2H), 7.45 (s, 1H), 7.17 (d, J = 20.4 Hz, 1H), 2.44 (s, 3H).13C NMR (126 MHz, DMSO) δ 166.28, 161.48, 152.81, 148.47, 147.11, 141.83, 138.22, 137.17, 135.22, 132.68, 130.21, 128.80, 128.67, 125.35, 124.82, 123.33, 119.72, 111.79, 111.25, 21.47.

4-Methyl-N-(2-(pyridin-3-yl)benzo[d]oxazol-5-yl)benzamide (4be)
Yield 73.5%; Pink solid; mp 186.4–186.9 °C; 1H NMR (500 MHz, DMSO) δ 10.45 (s, 1H), 9.39 (s, 1H), 8.84 (s, 1H), 8.57 (d, J = 7.2 Hz, 1H), 8.37 (s, 1H), 7.95 (d, J = 7.3 Hz, 2H), 7.84 (s, 2H), 7.69 (s, 1H), 7.39 (d, J = 7.4 Hz, 2H), 3.37 (s, 3H).13C NMR (126 MHz, DMSO) δ 165.96, 161.47, 152.81, 148.47, 147.09, 142.15, 141.83, 137.17, 135.22, 132.44, 129.43, 128.23, 124.82, 123.33, 119.75, 111.80, 111.23, 21.52.

N-(2-(Pyridin-3-yl)benzo[d]oxazol-5-yl)-2-naphthamide (4bf)
Yield 37.8%; Pink solid; mp 182.4–182.9 °C; 1H NMR (500 MHz, DMSO) δ 10.69 (s, 1H), 9.40 (s, 1H), 8.84 (s, 1H), 8.66 (s, 1H), 8.58 (d, J = 7.6 Hz, 1H), 8.43 (s, 1H), 8.10 (s, 4H), 7.88 (s, 2H), 7.68 (s, 3H).13C NMR (126 MHz, DMSO) δ 166.20, 161.53, 152.82, 148.49, 147.18, 141.88, 137.15, 135.23, 134.80, 132.66, 132.58, 129.46, 128.55, 128.36, 128.18, 127.38, 124.94, 124.82, 123.33, 119.74, 119.64, 111.84, 111.33.

4-Methoxy-N-(2-(pyridin-3-yl)benzo[d]oxazol-5-yl)benzamide (4bg)
Yield 55.3%; Pink solid; mp 204.9–205.3 °C; 1H NMR (500 MHz, DMSO) δ 10.34 (s, 1H), 9.38 (s, 1H), 8.83 (s, 1H), 8.56 (d, J = 6.8 Hz, 1H), 8.35 (s, 1H), 8.02 (s, 2H), 7.82 (s, 2H), 7.68 (s, 1H), 7.10 (s, 2H), 3.88 (s, 3H).13C NMR (126 MHz, DMSO) δ 165.50, 162.43, 161.43, 152.78, 148.46, 147.02, 141.82, 137.26, 135.19, 130.12, 127.33, 124.80, 123.33, 119.72, 114.12, 111.76, 111.18, 55.93.

N-(2-(Pyridin-3-yl)benzo[d]oxazol-5-yl)-3-(trifluoromethyl)benzamide (4bh)
Yield 72.6%; Pink solid; mp 127.3–127.8 °C; 1H NMR (500 MHz, DMSO) δ 10.73 (s, 1H), 9.39 (s, 1H), 8.85 (s, 1H), 8.59 (s, 1H), 8.36 (s, 2H), 8.02 (d, J = 7.4 Hz, 1H), 7.90–7.81 (m, 4H), 7.70 (s, 1H).13C NMR (126 MHz, DMSO) δ 164.65, 161.61, 152.86, 148.50, 147.36, 141.87, 138.72, 136.72, 136.24, 135.26, 132.37, 130.26, 129.82, 129.56, 128.68, 124.83, 123.29, 119.95, 112.15, 111.38.

N-(2-(Pyridin-3-yl)benzo[d]oxazol-5-yl)-4-(trifluoromethyl)benzamide (4bi)
Yield 42.7%; Pink solid; mp 179.8–180.4 °C; 1H NMR (500 MHz, DMSO) δ 10.72 (s, 1H), 9.39 (s, 1H), 8.84 (s, 1H), 8.56 (s, 1H), 8.37 (s, 1H), 8.22 (d, J = 7.6 Hz, 2H), 7.97 (d, J = 7.6 Hz, 2H), 7.85 (d, J = 8.8 Hz, 2H), 7.69 (s, 1H).13C NMR (126 MHz, DMSO) δ 164.99, 161.61, 152.85, 148.49, 147.35, 141.86, 139.15, 136.70, 135.24, 132.03, 131.78, 129.12, 125.90, 124.82, 123.28, 119.78, 111.98, 111.39.

2-Fluoro-N-(2-(pyridin-3-yl)benzo[d]oxazol-5-yl)benzamide (4bj)
Yield 32.6%; Pink solid; mp 208.6–209.1 °C; 1H NMR (500 MHz, DMSO) δ 10.68 (s, 1H), 9.39 (s, 1H), 8.84 (s, 1H), 8.57 (d, J = 6.9 Hz, 1H), 8.34 (s, 1H), 7.85 (d, J = 8.5 Hz, 1H), 7.77–7.63 (m, 4H), 7.40 (dd, J = 19.0, 8.9 Hz, 2H).13C NMR (126 MHz, DMSO) δ 163.35, 161.62, 160.37, 152.86, 148.50, 147.20, 141.91, 136.81, 135.25, 133.07, 130.42, 125.12, 124.82, 123.28, 119.02, 116.79, 116.62, 111.51, 111.12.

3-Fluoro-N-(2-(pyridin-3-yl)benzo[d]oxazol-5-yl)benzamide (4bk)
Yield 42.8%; Pink solid; mp 164.4–164.9 °C; 1H NMR (500 MHz, DMSO) δ 10.60 (s, 1H), 9.38 (s, 1H), 8.83 (s, 1H), 8.56 (d, J = 7.1 Hz, 1H), 8.36 (s, 1H), 7.90–7.82 (m, 4H), 7.65 (d, J = 24.3 Hz, 2H), 7.49 (s, 1H).13C NMR (126 MHz, DMSO) δ 164.73, 163.39, 161.54, 152.81, 148.47, 147.27, 141.83, 137.65, 136.78, 135.21, 131.12, 124.79, 124.42, 123.28, 119.78, 119.10, 115.11, 111.95, 111.31.

4-Fluoro-N-(2-(pyridin-3-yl)benzo[d]oxazol-5-yl)benzamide (4bl)
Yield 23.7%; Pink solid; mp 174.5–175.1 °C; 1H NMR (500 MHz, DMSO) δ 10.54 (s, 1H), 9.38 (s, 1H), 8.83 (s, 1H), 8.56 (d, J = 7.0 Hz, 1H), 8.35 (s, 1H), 8.12 (s, 2H), 7.83 (s, 2H), 7.68 (s, 1H), 7.42 (s, 2H).13C NMR (126 MHz, DMSO) δ 165.02, 163.60, 161.50, 152.78, 148.45, 147.18, 141.82, 136.97, 135.23, 131.72, 130.91, 124.81, 123.31, 119.78, 115.93, 111.91, 111.26.

4-Chloro-N-(2-(pyridin-3-yl)benzo[d]oxazol-5-yl)benzamide (4bm)
Yield 62.5%; Pink solid; mp 211.9–211.3 °C; 1H NMR (500 MHz, DMSO) δ 10.62 (s, 1H), 9.39 (d, J = 1.4 Hz, 1H), 8.86–8.83 (m, 1H), 8.58–8.56 (m, 1H), 8.36 (s, 1H), 8.07 (d, J = 8.5 Hz, 2H), 7.91 (d, J = 8.4 Hz, 1H), 7.84 (s, 1H), 7.70–7.66 (m, 2H), 7.41 (d, J = 8.3 Hz, 1H).13C NMR (126 MHz, DMSO) δ 165.07, 161.57, 152.84, 148.50, 147.28, 141.87, 135.24, 134.05, 131.39, 130.18, 128.99, 128.05, 124.82, 123.33, 119.84, 111.99, 111.31.

4-Bromo-N-(2-(pyridin-3-yl)benzo[d]oxazol-5-yl)benzamide (4bn)
Yield 27.6%; Pink solid; mp 263.0–263.8 °C; 1H NMR (500 MHz, DMSO) δ 10.57 (s, 1H), 9.38 (s, 1H), 8.84 (s, 1H), 8.56 (d, J = 7.0 Hz, 1H), 8.35 (s, 1H), 7.98 (d, J = 7.3 Hz, 2H), 7.82 (d, J = 13.6 Hz, 4H), 7.68 (s, 1H).13C

NMR (126 MHz, DMSO) δ 165.13, 161.54, 152.82, 148.48, 147.23, 141.84, 136.86, 135.22, 134.38, 131.92, 130.32, 125.90, 124.80, 123.29, 119.76, 111.91, 111.31.

N-(2-(Pyridin-3-yl)benzo[d]oxazol-5-yl)thiophene-2-carboxamide (4bo)
Yield 42.3%; Pink solid; mp 161.2–161.8 °C; 1H NMR (500 MHz, DMSO) δ 10.49 (s, 1H), 9.39 (s, 1H), 8.84 (s, 1H), 8.56 (s, 1H), 8.30 (s, 1H), 8.10 (s, 1H), 7.92 (s, 1H), 7.85 (d, J = 8.6 Hz, 1H), 7.78 (d, J = 8.7 Hz, 1H), 7.69 (s, 1H), 7.28 (s, 1H); 13C NMR (126 MHz, DMSO) δ 161.56, 160.50, 152.83, 148.49, 147.22, 141.88, 140.34, 136.59, 135.24, 132.46, 129.73, 128.58, 124.81, 123.30, 119.77, 111.94, 111.36.

N-(2-(Pyridin-4-yl)benzo[d]oxazol-5-yl)benzamide (4ca)
Yield 56.2%; Pink solid; mp 132.1–132.6 °C; 1H NMR (500 MHz, DMSO) δ 10.50 (s, 1H), 8.88 (d, J = 5.8 Hz, 2H), 8.40 (s, 1H), 8.17–8.10 (m, 2H), 8.03 (d, J = 7.2 Hz, 2H), 7.87 (s, 2H), 7.61 (dt, J = 12.2, 5.9 Hz, 3H).13C NMR (126 MHz, DMSO) δ 166.21, 161.42, 151.37, 147.29, 141.80, 137.26, 135.33, 133.97, 132.16, 128.93, 128.18, 121.28, 120.44, 112.05, 111.51.

2-Phenyl-N-(2-(pyridin-4-yl)benzo[d]oxazol-5-yl)acetamide (4cb)
Yield 67.7%; Pink solid; mp 120.5–120.9 °C; 1H NMR (500 MHz, DMSO) δ 10.52 (s, 1H), 8.86 (d, J = 6.1 Hz, 2H), 8.27 (s, 1H), 8.11 (d, J = 6.1 Hz, 2H), 7.82 (d, J = 8.9 Hz, 1H), 7.65 (d, J = 10.9 Hz, 1H), 7.42–7.34 (m, 4H), 7.29 (d, J = 7.0 Hz, 1H), 3.72 (s, 2H).13C NMR (126 MHz, DMSO) δ 169.76, 161.39, 151.37, 146.93, 141.85, 137.39, 136.38, 133.94, 129.67, 128.82, 127.06, 121.26, 119.15, 111.68, 110.62, 43.78.

2-Methyl-N-(2-(pyridin-4-yl)benzo[d]oxazol-5-yl)benzamide (4cc)
Yield 22.3%; Pink solid; mp 151.6–152.0 °C; 1H NMR (500 MHz, DMSO) δ 10.57 (s, 1H), 8.87 (s, 2H), 8.40 (s, 1H), 8.13 (d, J = 5.9 Hz, 2H), 7.84 (dd, J = 20.2, 8.8 Hz, 2H), 7.54 (d, J = 7.4 Hz, 1H), 7.44 (t, J = 7.2 Hz, 1H), 7.36 (t, J = 7.7 Hz, 2H), 1.94 (s, 3H).13C NMR (126 MHz, DMSO) δ 172.49, 168.44, 161.43, 151.40, 147.16, 141.84, 137.41, 135.78, 133.95, 131.07, 130.23, 127.75, 126.18, 121.27, 119.63, 111.64, 111.18, 21.55.

3-Methyl-N-(2-(pyridin-4-yl)benzo[d]oxazol-5-yl)benzamide (4cd)
Yield 26.9%; Pink solid; mp 189.1–189.7 °C; 1H NMR (500 MHz, DMSO) δ 10.47 (s, 1H), 8.88 (d, J = 6.0 Hz, 2H), 8.40 (s, 1H), 8.13 (d, J = 6.0 Hz, 2H), 7.87–7.79 (m, 4H), 7.50–7.41 (m, 2H), 2.45 (s, 3H).13C NMR (126 MHz, DMSO) δ 166.31, 161.41, 151.39, 147.24, 141.79, 138.26, 137.30, 135.34, 133.96, 132.74, 128.84, 128.66, 125.34, 121.27, 120.38, 111.98, 111.52, 21.47.

4-Methyl-N-(2-(pyridin-4-yl)benzo[d]oxazol-5-yl)benzamide (4ce)
Yield 73.2%; Pink solid; mp 193.6–194.0 °C; 1H NMR (500 MHz, DMSO) δ 10.44 (s, 1H), 8.87 (d, J = 6.0 Hz, 2H), 8.40 (s, 1H), 8.13 (d, J = 6.0 Hz, 2H), 7.95 (d, J = 8.1 Hz, 2H), 7.86 (s, 2H), 7.39 (d, J = 7.9 Hz, 2H), 2.43 (s, 3H).13C NMR (126 MHz, DMSO) δ 166.00, 161.38, 151.38, 147.21, 142.19, 141.78, 137.34, 133.97, 132.41, 129.45, 128.23, 121.27, 120.42, 111.99, 111.48, 21.52.

N-(2-(Pyridin-4-yl)benzo[d]oxazol-5-yl)-2-naphthamide (4cf)
Yield 37.8%; Pink solid; mp 178.6–178.9 °C; 1H NMR (500 MHz, DMSO) δ 10.69 (s, 1H), 8.88 (d, J = 5.9 Hz, 2H), 8.65 (s, 1H), 8.46 (d, J = 1.3 Hz, 1H), 8.16–8.03 (m, 6H), 7.91 (dt, J = 18.0, 5.3 Hz, 2H), 7.71–7.64 (m, 2H).13C NMR (126 MHz, DMSO) δ 166.24, 161.43, 151.35, 147.32, 141.84, 137.33, 134.83, 134.00, 132.63, 132.60, 129.46, 128.80, 128.56, 128.37, 128.19, 127.38, 124.93, 121.29, 120.46, 112.08, 111.55.

4-Methoxy-N-(2-(pyridin-4-yl)benzo[d]oxazol-5-yl)benzamide (4cg)
Yield 35.3%; Pink solid; mp 194.9–195.4 °C; 1H NMR (500 MHz, DMSO) δ 10.34 (s, 1H), 8.88 (d, J = 5.7 Hz, 2H), 8.39 (s, 1H), 8.17–8.11 (m, 2H), 8.03 (d, J = 8.8 Hz, 2H), 7.86 (s, 2H), 7.12 (d, J = 8.8 Hz, 2H), 3.88 (s, 3H).13C NMR (126 MHz, DMSO) δ 165.55, 162.49, 161.37, 151.38, 147.17, 141.79, 137.45, 133.99, 130.13, 127.31, 121.27, 120.44, 114.15, 111.99, 111.44, 55.95.

N-(2-(Pyridin-4-yl)benzo[d]oxazol-5-yl)-3-(trifluoromethyl)benzamide (4ch)
Yield 65.6%; Pink solid; mp 138.3–138.9 °C; 1H NMR (500 MHz, DMSO) δ 10.75 (s, 1H), 8.88 (d, J = 5.9 Hz, 2H), 8.36 (dd, J = 21.3, 13.1 Hz, 3H), 8.14 (d, J = 5.9 Hz, 2H), 8.03 (d, J = 7.7 Hz, 1H), 7.86 (dd, J = 20.6, 12.0 Hz, 3H).13C NMR (126 MHz, DMSO) δ 164.70, 161.53, 154.77, 151.40, 147.49, 141.81, 136.84, 136.15, 133.93, 132.38, 130.29, 129.84, 128.80, 124.81, 121.30, 120.63, 112.37, 111.65.

N-(2-(Pyridin-4-yl)benzo[d]oxazol-5-yl)-4-(trifluoromethyl)benzamide (4ci)
Yield 42.7%; Pink solid; mp 189.8–190.4 °C; 1H NMR (500 MHz, DMSO) δ 10.71 (s, 1H), 8.86 (d, J = 6.0 Hz, 2H), 8.39 (s, 1H), 8.21 (d, J = 8.1 Hz, 2H), 8.11 (d, J = 6.0 Hz, 2H), 7.95 (d, J = 8.3 Hz, 2H), 7.86 (s, 2H).13C NMR (126 MHz, DMSO) δ 164.99, 161.48, 151.35, 147.44, 141.78, 139.09, 136.86, 133.89, 132.06, 129.12, 125.89, 123.32, 121.25, 120.43, 112.17, 111.60.

2-Fluoro-N-(2-(pyridin-4-yl)benzo[d]oxazol-5-yl)benzamide (4cj)
Yield 47.8%; Pink solid; mp 221.2–221.5 °C; 1H NMR (500 MHz, DMSO) δ 10.69 (s, 1H), 8.88 (d, J = 5.5 Hz, 2H), 8.38 (s, 1H), 8.14 (d, J = 5.6 Hz, 2H), 7.88 (d, J = 8.8 Hz, 1H), 7.82–7.73 (m, 2H), 7.64 (d, J = 6.6 Hz, 1H), 7.40 (dd, J = 19.6, 8.8 Hz, 2H).13C NMR (126 MHz, DMSO) δ 163.39, 161.54, 151.41, 147.33, 141.86, 136.98, 133.92, 133.18, 130.45, 125.42, 125.11, 121.29, 119.72, 116.81, 116.63, 111.77, 111.35.

3-Fluoro-N-(2-(pyridin-4-yl)benzo[d]oxazol-5-yl)benzamide (4ck)
Yield 32.8%; Pink solid; mp 163.3–163.8 °C; 1H NMR (500 MHz, DMSO) δ 10.67 (s, 1H), 8.88 (d, J = 4.1 Hz, 2H), 8.38 (s, 1H), 8.14 (d, J = 4.2 Hz, 2H), 7.88 (d, J = 8.7 Hz, 1H), 7.81–7.73 (m, 2H), 7.64 (d, J = 5.8 Hz, 1H), 7.40 (dd, J = 17.4, 9.2 Hz, 2H).13C NMR (126 MHz, DMSO) δ 163.39, 161.54, 151.40, 147.35, 141.87, 136.98, 133.93, 133.17, 133.10, 130.43, 125.12, 121.29, 119.75, 116.80, 116.62, 111.75, 111.39.

4-Fluoro-N-(2-(pyridin-4-yl)benzo[d]oxazol-5-yl)benzamide (4cl)
Yield 23.7%; Pink solid; mp 154.6–155.1 °C; 1H NMR (500 MHz, DMSO) δ 10.54 (s, 1H), 8.88 (d, J = 5.9 Hz, 2H), 8.39 (s, 1H), 8.15–8.09 (m, 4H), 7.87 (d, J = 7.4 Hz, 2H), 7.43 (t, J = 8.8 Hz, 2H).13C NMR (126 MHz, DMSO) δ 165.08, 161.44, 151.39, 147.31, 141.79, 137.13, 133.94, 131.73, 130.90, 121.27, 120.47, 115.97, 115.79, 112.11, 111.55.

4-Chloro-N-(2-(pyridin-4-yl)benzo[d]oxazol-5-yl)benzamide (4cm)
Yield 34.5%; Pink solid; mp 216.5–217.0 °C; 1H NMR (500 MHz, DMSO) δ 10.60 (s, 1H), 8.87 (d, J = 4.5 Hz, 2H), 8.38 (s, 1H), 8.12 (d, J = 5.8 Hz, 2H), 8.05 (d, J = 8.5 Hz, 2H), 7.86 (s, 2H), 7.66 (d, J = 8.5 Hz, 2H).13C NMR (126 MHz, DMSO) δ 165.07, 161.45, 151.37, 147.37, 141.80, 137.08, 136.99, 134.02, 133.94, 130.16, 128.99, 121.27, 120.50, 112.18, 111.53.

4-Bromo-N-(2-(pyridin-4-yl)benzo[d]oxazol-5-yl)benzamide (4cn)
Yield 17.6%; Pink solid; mp 268.1–268.7 °C; 1H NMR (500 MHz, DMSO) δ 10.55 (s, 1H), 8.86 (s, 2H), 8.37 (s, 1H), 8.11 (d, J = 5.7 Hz, 2H), 7.97 (d, J = 8.4 Hz, 2H), 7.86–7.77 (m, 4H).13C NMR (126 MHz, DMSO) δ 165.17, 161.43, 151.36, 147.34, 141.78, 137.01, 134.33, 133.91, 131.93, 130.32, 125.95, 121.26, 120.42, 112.11, 111.54.

N-(2-(Pyridin-4-yl)benzo[d]oxazol-5-yl)thiophene-2-carboxamide (4co)
Yield 62.8%; Pink solid; mp 162.4–162.8 °C; 1H NMR (500 MHz, DMSO) δ 10.48 (s, 1H), 8.88 (d, J = 6.0 Hz, 2H), 8.34 (s, 1H), 8.14 (d, J = 4.5 Hz, 2H), 8.09 (d, J = 3.6 Hz, 1H), 7.90 (dd, J = 18.6, 7.3 Hz, 2H), 7.81 (d, J = 8.9 Hz, 1H), 7.31–7.27 (m, 1H).13C NMR (126 MHz, DMSO) δ 161.49, 160.54, 151.40, 147.36, 141.84, 140.29, 136.76, 133.95, 132.53, 129.77, 128.60, 121.30, 120.47, 112.17, 111.63.

5.1.3. Structure Determination
Single-crystal X-ray diffraction was used to determine the crystal structures of 4ac–4bc. The chemical 4ac–4bc was dissolved in 3 mL of ethyl acetate to a total weight of 100 mg. The resulting solution was then transferred into a 25 mL micro-reaction container. After the reaction container was put into a sealed petroleum ether dryer, the dryer was closed.[11] The single-crystal culture was finished after three days when the reaction bottle was removed. On a Bruker APEX II area detector diffractometer fitted with graphite-monochromatic MoK radiation (λ = 0.71073A°) at 296(2)K using the ω–2θ scan mode, reflection measurements were obtained at room temperature. SADABS was used to apply empirical adsorption adjustments to all of the data. Using SHELXTL 97 software, the structures were solved directly and then polished using full matrix least squares on F2. Through direct procedures and later difference Fourier syntheses, all non-hydrogen atoms were found. Geometrical calculations were used to find the hydrogen atoms bonded to carbon, and during the structural refinement in 4ac–4bc, their locations and thermal characteristics were set. Supplementary Materials contains essential information and crystallographic data.

5.2. Anti-Fungal Activity
Here, using the inhibition zone method at a concentration of 100 μg/mL by poisoned food technique, the antifungal activities of these compounds were assessed against eight common phytopathogenic fungi: Fusarium solani, Colletotrichum gloeosporioides, Mycosphaerella melonis melonis, Alternaria brassicae, Pyricularia grisea, Curvularia lunata, Alternaria solani, and Fusarium graminearum. Inoculate the potato dextrose agar (PDA) plate: Using a petri dish, uniformly distribute the potato dextrose agar (PDA) culture solution without any substances to be tested (blank controls) and let it cool and solidify.[12] Similarly, the chemical to be tested was mixed with potato dextrose agar (PDA) culture solution at varying concentrations, and the mixture was uniformly placed onto the petri dish until it cooled and hardened. Next, each cold petri dish was inoculated with colonies from 24-hour-old potato dextrose agar (PDA) petri plates using a sterile drill to create 5 mm holes. Among these, the DMSO content had to be less than 2% of the total solution volume, and the stock solutions for in vitro research had a concentration of 400 μg/mL. Commercially available agricultural fungicide thiophanate-methyl was used as a positive control, whereas the solution without the test chemical served as a blank control. Additionally, petri dishes were cultured in a light incubator for 5-7 days under appropriate growing conditions. Every experiment was conducted three times independently.

CONCLUSION

Through the use of benzoxazole derivatives' synthetic plasticity and pharmacological potential, this study aims to facilitate the creation of new antifungal medicines that exhibit enhanced effectiveness and decreased susceptibility to resistance. In the end, this study's results could open the door to the creation of fresh treatment approaches for the control of fungal infections, filling a gap in the field and enhancing patient outcomes.

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